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Fever, Leukopenia, and Thrombocytopenia in a Patient with Acute Lyme Borreliosis Were Due to Human Granulocytic Ehrlichiosis

SIR—Günthard et al. [1] raised the question whether leukopenia, thrombocytopenia, and hepatitis may be associated with acute Lyme borreliosis. The authors described a 22-year-old man who presented with fever, headache, myalgia, arthralgia, conjunctivitis, fatigue, and erythema migrans after he had been camping in forests in Slovenia. Because of the presence of leukopenia and thrombocytopenia, a diagnosis of ehrlichiosis was considered, but serological tests to detect antibodies to *Ehrlichia equi* and *Ehrlichia phagocytophila* and microscopic examination of blood smears were negative. However, the presence of antibodies to *Borrelia burgdorferi* was documented. The patient was treated with tetracyclines and recovered quickly.

Nadelman et al. [2] challenged the assertion of Günthard et al. [1, 3], arguing that a negative serology for *E. equi* does not exclude coinfection with *Ehrlichia* and that unusual clinical manifestations or laboratory findings following tick bites are not necessarily due to the protean manifestations of Lyme borreliosis but may be caused by coinfection with *B. burgdorferi* and the agents of human granulocytic ehrlichiosis (HGE), babesiosis, or tick-borne encephalitis.

We recently had the opportunity to follow the patient of Günthard almost 2 years after his illness. He had been completely healthy since he was treated for acute Lyme disease. In addition, he clearly remembered that he had been bitten by several ticks in Slovenia. Three stored serum samples (kindly provided by Dr. O. Péter, Sion, Switzerland) and one specimen obtained during the current follow-up were examined for antibodies to *E. phagocytophila* by indirect immunofluorescence, as previously described [4]. We found seroconversion and reconversion of antibodies to *E. phagocytophila,* suggesting that the patient had been coinfected with the agent of HGE and with *B. burgdorferi* (table 1). It is well accepted that the causative agent of HGE is immunologically closely related to *E. phagocytophila* and *E. equi,* and thus these antigens (but not the *Ehrlichia chaffeensis* antigen) are useful in serological testing for HGE [6].

Ticks of the genus *Ixodes* (the likely vector of HGE) are prevalent in Europe and are known to transmit Lyme borreliosis and the European tick-borne encephalitis virus. In addition, seroepidemiological

Table 1. Laboratory values for a 22-year-old man who was bitten by a tick in Slovenia.

	No. of days after tick bite					
Parameter	7	9	12	21	90	620
Leukocytes ($\times 10^9$/L)	2.2	3.3	ND	4.3	ND	ND
Thrombocytes ($\times 10^9$/L)	98	140	ND	228	ND	ND
C-reactive protein (mg/L)*	59	16	ND	ND	ND	ND
Aspartate aminotransferase (U/L)†	96	61	ND	16	ND	ND
Alanine aminotransferase (U/L)†	91	109	ND	51	ND	ND
IgG and IgM antibodies to *Borrelia burgdorferi*‡	Negative	ND	Positive	Positive	ND	ND
IgM antibodies to *B. burgdorferi*‡	Borderline	ND	Positive	Positive	ND	ND
Antibodies to European tick-borne encephalitis virus	Negative	ND	ND	Negative	Negative	ND
Antibodies to *Ehrlichia equi* and *Ehrlichia phagocytophila*‡	Negative	ND	ND	Negative	Negative	ND
Titer of antibodies to *E. phagocytophila*§	<20	ND	80	ND	80	<20

NOTE. ND = not done.
* Normal level, <10.
† Normal level, <40.
‡ Data are from [1,3].
§ Data are from methods previously described [4,5]; titers of <80 are considered negative.

data from Switzerland [7], Norway, the United Kingdom, and Sweden have suggested that HGE may be prevalent in Europe. Investigators in Slovenia recently provided serological and molecular evidence of HGE in their country [8]. Furthermore, a newly discovered species of *Ehrlichia* in dogs in Switzerland was shown to have a 100% sequence homology of the 16S rRNA gene with that of the agent of HGE [9]. Thus, it can be hypothesized that HGE occurs in Europe, although there have not been any reports of microscopic detection of the organism in humans.

The methods for diagnosing HGE have yet to be improved. The clinical manifestation of ehrlichiosis is a nonspecific febrile illness. The sensitivity of microscopic examination for detecting *Ehrlichia* in granulocytes or monocytes is low [10], and molecular diagnosis is available only in research laboratories. Serological tests to detect antibodies to the agent of HGE are currently not standardized and are not commercially available; furthermore, negative serological tests do not exclude the presence of ehrlichiosis. We believe that the failure of Günthard et al. [1, 3] to detect antibodies reacting with *E. equi* and *E. phagocytophila* on days 21 and 90 could be explained by a somewhat lower diagnostic sensitivity of the tests used. We have used an assay that has been extensively validated in 2,557 serum samples from cattle [4], 1,645 serum samples from horses [5], and in 1,515 human serum samples (N. Pusterla, unpublished data).

Epidemiological and clinical evidence is growing that HGE is also prevalent in Europe. Suspicion of HGE (or dual infections with HGE and Lyme borreliosis), based on a patient's history and clinical presentation and the pathognomonic laboratory pattern, including leukopenia, thrombocytopenia, and elevation of transaminases [10], is crucial because it has major therapeutic implications. HGE requires treatment with tetracyclines and does not respond to β-lactam antibiotics [10].

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